55. (New) The pharmaceutical composition according to claim 20, wherein the salt is an alkali metal or alkaline earth metal salt and the E protein is a deleted E protein.

56. (New) The pharmaceutical composition according to claim 20, wherein the pH is adjusted using a buffer and the E protein is a deleted E protein.

57. (New) The pharmaceutical composition according to claim 30 in the form of a combination vaccine, wherein the papillomaviruses are selected from HPV-16 and HPV-18 or HPV-18, HPV-31, HPV-45 and HPV-58 or HPV-6 and HPV-11 and the E protein is a deleted E protein.--

REMARKS

Status of the Claims

By this amendment, claims 1-15 are canceled and claims 16-57 are added. Accordingly, upon entry of this Amendment, claims 16-57 will be pending in the application.

Support for newly added claims 16-57 is found in the present specification. For example, support for claim 16 is found in originally filed claim 1. Support for claim 17 is found in originally filed claim 2. Support for claim 18 is found in originally filed claim 3. Support for claim 19 is found in originally filed claim 1. Support for claim 20 is found in originally filed claim 4. Support for claim 21 is found in originally filed claim 5. Support for claim 22 is found in originally filed claim 6. Support for claim 23 is found in originally filed claim 7. Support for claim 24 is found in originally filed claim 8. Support for claim 25 is found in originally filed claim 9. Support for claim 26 is found in originally filed claim 10. Support for claim 27 is found in originally filed claim 11. Support for claim 28 is found in originally filed claim 12. Support for claim 29 is found in originally filed claim 13. Support for claim 30 is found in originally filed claim 14. Support for claim 31 is found in originally filed claim 15. Support for claims 32-35 is found in the present specification on page 5, lines 27-30. Support for claims 36-38 is found in the present specification on page 6, lines 7-10. Support for claim 39 is found in the present specification on page 6, lines 12-18. Support for claims 40-41 is found in the present specification on page 7, lines 14-16. Support for claims

42-43 is found in the present specification on page 7, lines 20-22. Support for claims 44-45 is found in the present specification on page 7, lines 24-25. Support for claims 46-51 is found in originally filed claims 2-6 and 15, respectively, and in originally filed claim 7. Support for claims 52-57 is found in originally filed claims 2-6 and 15, respectively, and in originally filed claim 10. Claims 16-57 are added to clearly define claim scope. No new matter is added.

Issues Under Sequence Compliance

The Examiner objects to the specification. The Examiner states that Applicant must append SEQ ID NOS to all mentions of specific sequences in the specification. Applicants have amended the specification to recite SEQ ID NOS on page 14, lines 12 and 14; page 15, lines 1, 3 and 15-18; and page 16, lines 5, 7-8, 10-11 and 16.

Issues Under Specification

The Examiner objects to the specification because there is no brief description of drawing number 5 shown in table 1. The Examiner also objects to the amendment submitted on February 19, 2001 because part of the amendment to the specification has been hand-written. Applicants have amended the specification appropriately and respectfully request withdrawal of the objections.

Issues Under Priority

The Examiner notes that Applicants have not filed a certified copy of the instant application as required by 35 U.S.C. § 119(b). Attached herewith as Exhibit 1 is a certified copy of the German priority document dated March 24, 1998. Also attached is an English translation of this document.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 1-15 are rejected by the Examiner Under 35 U.S.C. § 112, second paragraph as being indefinite.

The Examiner asserts that claim 1 is drawn to "avoidance" of the papillomavirus. The Examiner states that it is assumed that Applicant intends to prevent papillomavirus tumor development since there is no way to avoid exposure to the virus. New claim 16 (which is similar to originally filed claim 1) recites "...wherein the pharmaceutical composition is capable of preventing or treating human papillomavirus (HPV)-specific tumor." Support is found throughout the present specification. For example, support is found on page 8, lines 5-7 and on page 13, line 23. The term "avoidance" is not present in new claims 16-57.

The Examiner also asserts that in claim 1, the phrase "if appropriate" renders the claim indefinite. The phrase "if appropriate" is not recited in new claims 16-57.

The Examiner further asserts that in claim 1, it is unclear whether the additives are supposed to be devoid of papillomavirus epitopes or if the fusion protein containing L1 and E have no unspecific epitopes. Claim 16 (which is similar to originally filed claim 1) recites "...wherein the fusion protein contains no papillomavirus - unspecific epitopes" and does not recite "...and, if appropriate, suitable additives and/or excipients", thus eliminating confusion regarding whether the additives are supposed to be devoid of papillomavirus epitopes or if the fusion protein containing L1 and E have no unspecific epitopes.

The Examiner asserts that claims 7 and 10 are drawn to the L1 or the E proteins being deleted proteins. The Examiner questions whether a portion of the L1 or E protein is deleted or whether the L1 or E proteins are deleted from a papillomavirus. New claims 23 and 26 correspond to originally filed claims 7 and 10. Applicants believe that the specification clearly indicates that the expression "deleted protein" refers to a protein of which parts of the amino acid sequences have been deleted. Applicants direct the Examiner's attention to page 7, paragraphs 2 and 3 of the present specification. For example, on page 7, lines 14-16, it states that up to 35 amino acids may be deleted from the C terminal of the L1 protein.

Finally, the Examiner asserts that in claim 9, there is insufficient antecedent basis for the limitation "L" in line 11. New claim 25 corresponds to originally filed claim 9 and recites L1 instead of L. This change merely corrects a typographical error and does not narrow the scope of the claim.

Claim Rejections - 35 U.S.C. § 102

Claims 1 and 7-14 are rejected by the Examiner under 35 U.S.C. § 102 (b) as being anticipated by Muller et al. Applicants respectfully traverse and request reconsideration and withdrawal of the rejection.

The Present Invention

Claim 16 of present invention is directed to a pharmaceutical composition which is capable of preventing or treating human papillomavirus-specific tumor.

Muller et al.

Muller et al. teaches chimeric papillomavirus-like particles (CVLPs).

Distinctions Over the Cite Art

The present invention is not anticipated by Muller et al. because Muller et al. fails to teach a pharmaceutical composition of CVLPs that exists in a form capable of preventing or treating human papillomavirus-specific tumors. The Examiner asserts that in the last paragraphs of the first and second columns on page 108 of Muller et al., Muller et al. teaches that the chimeric CVLPs of the present invention "could be useful as a therapeutic and prophylactic vaccine and predicts that these particles will be able to induce a CTP response based on some preliminary data indicating that CTLS can be induced in mice after immunization." Applicants note that Muller et al. provide no data with respect to CVLPs adequate to establish a reasonable expectation of success in preventing or treating HPV-specific tumors. On page 108, Muller describes the interaction of CVLPs and host cells by incubating kidney epithelial cells with particles generated by the construct HPV 16 L1ΔC*; however, Muller et al. does not provide any enabling data relating to preventing or treating human papillomavirus (HPV)-specific tumor and the form of CVLPs used in Muller for such an in vitro test inherently would not be the same as the claimed compositions for therapeutic use in a mammal.

Furthermore, Applicants note that the last paragraphs of the first and second columns on page 108 of Muller et al. as well as the second paragraph of the first column on page 93 of

Muller et al. are only directed to CVLPs in general or to human papillomaviruses in general. These passages do not refer to the pharmaceutical compositions of the invention, i.e. to pharmaceutical compositions comprising at least one fusion protein of at least one L1 and at least one E protein of one or more papillomaviruses.

Applicants recognize that a preamble may not distinguish a claimed product over the prior art. However, the preamble of this invention is tied to a functional limitation requiring that the pharmaceutical composition of the present invention is "capable of preventing or treating human papillomavirus (HPV)-specific tumor." Therefore, this means that the claimed pharmaceutical composition is physically not the same as the composition of Muller et al.

In view of the above discussion, the present invention is not anticipated by Muller et al.

Claim Rejections - 35 U.S.C. § 103

Claims 2-6 and 15 are rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Muller et al. as applied to claims 1 and 7-13, and further in view of Hines et al. The Examiner asserts that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because of the teachings of Muller et al. to produce CVLPs that incorporate an E protein and the prophylactic and adjuvant-like stimulatory effects of papillomavirus subunit vaccines taught by Hines et al. Applicants respectfully traverse and request reconsideration and withdrawal of the rejection.

The Examiner has failed to establish a *prima facie* case of obviousness because all three of the criteria required to establish a *prima facie* case of obviousness have not been met. In order to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.

Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. See MPEP 2142.

The Examiner has failed to establish a *prima facie* case of obviousness because a person of ordinary skill in the art would not have had a reasonable expectation of success in combining the teachings of Muller et al. and Hines et al. to arrive at the present pharmaceutical composition which is capable of preventing or treating human papillomavirus (HPV)-specific tumor. Muller et al. teach that the CVLPs described therein can be internalized by monkey kidney epithelial cells. Muller et al. do not provide any clinical data reporting the efficacy of CVLPs for preventing or treating human papillomavirus (HPV)-specific tumor. Therefore, a person of ordinary skill in the art would not have been motivated to consider the possibility that the pharmaceutical composition of the present invention would be successful in the prevention or treatment of human papillomavirus-specific tumors.

Hines et al. does not cure the deficiencies of Muller et al. In fact, Hines et al. teach that the state of the art regarding prophylactic or therapeutic vaccines against human papillomavirus was extremely unpredictable, challenging and undeveloped. For example, there is a section titled "Prophylactic vaccines" on pages 16 and 17 of Hines et al. On page 16, right column, last paragraph, first sentence of Hines et al. it states:

> "There are, however, numerous challenges which must be addressed."

There is also a section titled "Therapeutic vaccines" on page 17 of Hines et al. On page 17, left column, fourth paragraph, first sentences of Hines et al. it states:

> "Similar challenges plague the development of these various strategies". (i.e. the development of vaccines).

Therefore, Hines et al. conclude that at the publication date of their paper, vaccines against human papilloma-specific tumors were not yet available and many difficulties would have to be overcome in order to produce such vaccines.

There would have been no expectation of success for a person of ordinary skill in the art at the time the present invention was made to make effective vaccines involving chimeric CVLPs capable of prevention or treatment of human papillomavirus-specific tumors. The teaching of Muller et al., in view of Hines et al., constitutes at best the expression of the hope that in the future it will be possible to produce vaccines against human papillomavirus-specific tumors. Therefore, the present invention is not obvious over Muller et al. in view of Hines et al.

Further evidence supporting the fact that the state of the art regarding vaccines against human papillomavirus was unpredictable and uncertain is attached herewith as Exhibits 2 (Rudolf, M. et al. (1999) *Biol. Chem.*,**380**, 335-340), 3 (Toes, R. et al. (1996) *Proc. Natl. Acad. Sci. USA*, **93**, 7855-7860) and 4, (Toes, R. et al. (1995) *The Journal of Immunology*, **154**, 3396-3405). These publications demonstrate that it would have been impossible for a person of ordinary skill in the art to predict whether the pharmaceutical composition of the present invention would be capable of preventing or treating human papilloma (HPV) - specific tumor (claim 16). None of these publications (nor those cited in the Office Action) show the effectiveness of the presently claimed composition *in vivo*. Since the field was so unpredictable and uncertain and since Muller et al. did not present any clinical data showing the effectiveness of the CVLPs *in vivo*, the present invention would not have been obvious to a person of ordinary skill in the art.

In Rudolf et al., induction of HPV16 capsid protein-specific human T-cell responses by virus-like particles is examined. Figure 2 on page 336 shows a comparison of the ability of VLPs and capsomeres to induce a cytotoxic immune response. The proliferation of peripheral blood lymphocytes (PBL) demonstrated by ^{3}H-thymidine incorporation was examined in order to measure activation of cytotoxic T-cells. Figure 2 demonstrates that L1-VLP as well as L1L2-VLP are able to induce a cytotoxic T-cell response. Figure 2 also demonstrates that L1-capsomeres are not able to induce a cytotoxic T-cell response. L1-VLP and L1-capsomeres differ from each other in one amino acid (Cys 152 to Ser). This demonstrates that the exchange of even one single amino acid is relevant for the induction of a cytotoxic immune response and also demonstrates unpredictability.

In Toes et al. (1996), the unpredictable observation is shown that vaccination with a peptide has a tumor promoting effect, rather than a protective effect.

Finally, Toes et al. (1995) show that the expression of the ras-oncogene can result in loss of the sensitivity against a cytotoxic T-cell response (see Figure 6, discussion on page 3404, first paragraph). It might be that a different intracellular processing of the antigen in the presence of the activated oncogene is responsible for this effect (page 3404, left column, lines 11 ff). The authors conclude "Because activated ras oncogenes have been strongly implicated in the development of human cancer, modulation of T-cell epitopes by ras-induced mechansims may be instrumental in the failure of T-cell immunity against malignant tumors in humans" (page 3404, left column, end of first paragraph). This publication clearly demonstrates that if one demonstrates the internalization of an antigen (as Muller et al. showed in monkey kidney epithelial cells), it cannot be concluded that the antigen may be capable of producing an effective cytotoxic T-cell response.

Claims 46-57

Claims 46-57 are not obvious over Muller et al. in view of Hines et al. Claims 46-57 contain the subject matter of originally filed claims 2-6 and 15. However, claims 46-57 also recite subject matter from claim 7 or 10, which claims were not rejected as being obvious over Muller et al. in view of Hines et al. Therefore, new claims 46-57 are not obvious over Muller et al. in view of Hines et al.

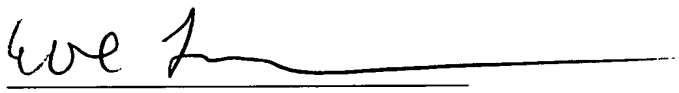
CONCLUSION

As the above-presented amendments and remarks address and overcome all of the rejections presented by the Examiner, withdrawal of the rejections and allowance of the claims are respectfully requested.

If the Examiner has any questions concerning this application, he or she is requested to contact the undersigned.

Respectfully submitted,

Date August 20, 2001

By 

Eve L. Frank
Registration No. 46,785

FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109
Telephone: (202) 945-6142
Facsimile: (202) 672-5399

Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

MEDICAMENT FOR THE AVOIDANCE OR TREATMENT OF PAPILLOMAVIRUS-SPECIFIC TUMOUR

This application is a continuation of PCT/EP99/01996, filed March 24, 1999, which claims the benefit of priority of a German application No. 198 12 941.6, filed March 24, 1998, the contents of each being expressly incorporated herein by reference.

The present invention relates to a medicament for the avoidance or treatment of human papillomaviruses (HPV)-specific tumour comprising at least one fusion protein from at least one L1 protein of one or more papillomaviruses and at least one E protein of one or more papillomaviruses and, if appropriate, suitable additives and/or excipients, the fusion protein containing no papillomavirus-unspecific epitopes.

Fig. 4 shows the prevention of the growth of TC-1 tumour by $L1E7_{1-60}$ CVLPs. 6×10^4 TC-1 tumour cells per mouse were inoculated into the left flank of C57BL/6 mice (5 per group). Two weeks later, the mice were immunized with an s.c. injection of 10 µg of $L1E7_{1-60}$ CVLPs (triangles), 10 µg of L1ΔCVLPs (circles) or HBS buffer (squares).

Fig. 5 shows tumor protection in C57BL16 mice by L1 $\Delta CE7_{1-60}$ CVLPs. Two weeks after innoculation of $6x10^4$ TC-1 cells, the mice received a single injection of L1 $\Delta CE7_{1-60}$ CVLPs. The mice were analyzed for the presence of tumors.

Examples

1. Preparation of chimeric genes coding for HPV16L1E7 fusion proteins

The HPV-16L1 open reading frame (ORF) was excized from the plasmid HPV-16-l14/k-L1/L2-pSynxtVI (Kirnbauer, R. et al. (1994) J. Virol. 67, 6929) using the restriction endonuclease BglII and cloned into the BamHI site in the vector pUC19 (New England Biolabs).

For the preparation of HPV-16L1ΔC, two primers were constructed which are complementary to HPV-16L1 ORF. The first primer has the sequence AAAGATATCTTGTAGTAAAAATTTGCGTCCTAAAGGAAAC (SEQ ID NO:1) and the second primer AAAGATATCTAATCTACCTCTACAACTGCTAAACGCAAAAAACG. (SEQ ID NO:2)

For the cloning of the fragment, primers having a 5'EcoRV restriction enzyme cleavage site were used. The following primer pair was used:
AAAAGATATCATGCATGGAGATACACCTACATTGC (SEQ ID NO:3)
and
TTTTGATATCGGCTCTGTCCGGTTCTGCTTGTCC. (SEQ ID NO:4)

P1: GTTATGACATACATACATTCTATG (L1) (SEQ ID NO:5)
P2: CCATGCATTCCTGCTTGTAGTAAAAATFTGCGTCC (E7) (SEQ ID NO:6)
P3: CTACAAGCAGGAATGCATGGAGATACACC(E7) (SEQ ID NO:7)
P4: CATCTGAAGCTTAGTAATGGGCTCTGTCCGGTTCTG (E7) (SEQ ID NO:8)

P5: CATCTGAAGCTTATCAATAUGTAATGGGCTCTGTCCG (E7 1-55) (SEQ ID NO:9)
P6:
CATCTGAAGCTTACTTGCAACAAAAGGTTACAATATTGTAATGGGCTCT
GTCCG (E7 1-60) (SEQ ID NO:10)
P7:
CATCTGAAGCTTAAAGCGTAGAGTCACACTTGCAACAAAAGGTTACAA
TATTGTAATGGGCTCTGTCCG (E7 1-65). (SEQ ID NO:11)

HPV16LlΔC*E7 1-70 was prepared using the clone HPVl6LlΔC*E7 1-65 and the primers P1 and P8.

P8:

CATCTGAAGCTTATTGTACGCACAACCGAAGCGTAGAGTCACACTTG (SEQ ID NO:12)